REMARKS

The Office Action mailed September 9, 2002 has been received and carefully considered. Applicants appreciate the Examiner's comments regarding claim priority, the missing sequence listing and abstract. Applicants have provided a sequence listing per 37 C.F.R. 1.821 through 1.825 and an abstract on a separate sheet as requested. Applicants have also requested the Examiner kindly insert a statement concerning the Cross Related Applications to clarify the priority of the application. No new matter is added as a result of these amendments. Support for the changes may be found for instance on page 17, line 5 through page 19, line 7, page 9, line 8 through page 10, line 21, and throughout the application as originally filed. Claims 5, 10, 14, 15, 24, and 37 stand withdrawn from consideration as non-elected species and claims 6, and 31-33 stand withdrawn from consideration as being drawn to non-elected subject matter. Applicants believe the current amended claims and remarks below address the Examiner's remaining concerns. Additionally, a copy of an Abstract is attached as Appendix C.

Claims 30 and 38 were objected to due to improper multiple dependency and the use of the phrase "regulating inhibition" respectively. These objections have been addressed through amendment/discussed below.

Claims 34-36 were rejected under 35 U.S.C. § 112 and § 101, as being indefinite and not "setting forth any steps involved in the process." Claims 11-13, 16, 21-23, and 38 were rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

Claims 1-4, 7-9, and 21-23 were rejected under 35 U.S.C. §102(b) as anticipated by the Maenpaa et al. article (Biochemical Pharmacology, Vol. 48, No. 7. pp. 1363-1369 (1994)). Claims 11-13 and 16 were rejected 35 U.S.C. §102(b) as anticipated by the Garnitskij et al. (SU 1803032, based on an oral translation). Claims 7-9, 21-23, and 34-36 were rejected under 35 U.S.C. § 102(b) as being anticipated by the Mays et al. article (Clin. Pharmacol. Ther., Vol. 42, No. 6, pp. 621-626 (1987)).

Claim 38 was rejected under 35 U.S.C. § 103(a) as being obvious over Garnitskij et al. in view of Modi et al. (U.S. 5,653,987).

The rejections, to the extent applied against the claims as amended, are respectfully traversed.

Objections

Claim 30 has been amended to address the multiple dependency.

Claim 38, according the USPTO should read, "inhibiting the metabolism" rather than "regulating inhibition." Applicants thank the Examiner for the suggestion and have amended the claim to reflect the language found in the specification. Therefore, Applicants respectfully request the USPTO withdrawal the objection.

Rejections Under 35 U.S.C. § 101

Claims 34-36 which stand rejected under 35 U.S.C. § 101 have been canceled and the rejection is therefore moot.

Rejections Under 35 U.S.C. § 112 ¶2

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-13, 16, 21-23 and 38 stand rejected under 35 U.S.C. § 112, second paragraph, as containing subject matter which fails to particularly point out and distinctly claim the invention. Applicants appreciate the Examiner's suggestions and believe that the claim amendments now provide the proper antecedent basis and further clarifying the claimed invention without altering the scope of the claims.

Applicants respectfully request that this rejection be withdrawn in view of the claim amendments.

35 U.S.C. §102(b)

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in a public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Applicants submit that the amendment to claims 2, 11, 21, 38 and those which depend there from have obviated the rejections submitted by the Examiner. The claimed invention is directed toward a compositions or methods for regulating the metabolism of nicotine. To constitute anticipation, all material elements of the claim must be found in one prior art source. (*In re Marshall*, 577 F.2d 301, 198 U.S.P.Q. 344 (CCPA 1978)). Likewise, a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (*Verdegaal Bros. v. Union Oil Co. of*

California, 814 F.2d 628, 631; 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). The rejections, to the extent applied against the claims as amended, are respectfully traversed.

Applicants provide further explanation as to why the references no longer apply to the claims as amended. On page 6 of the Office Action, claims 1-4, 7-9, and 21-23 were rejected under 35 U.S.C. §102(b) because "Maenpaa et al. discloses studies to determine the effect of methoxsalen on coumarin 7-hydroxylation in humans by administering 45 mg of a compositions comprising methoxsalen to five human subjects." Applicants contend the reference does not suggest that such a pharmaceutical composition could regulate the metabolism of nicotine to cotinine as required by the claim. As claim 2, now depends on none rejected claims 11 or 17, with regard to this reference the rejection is respectfully obviated and Applicants request the rejection be withdrawn.

The Examiner also rejected claims 21-23, using the same reference. Applicants contend that claim 21 is directed to a pharmaceutical composition comprising an effective amount of a composition to regulate the metabolism of nicotine to cotinine wherein the composition comprises at least two substances, at least one substance which selectively inhibits CYP2A6 and at least one substance which inhibits CYP2B6. Applicants, respectfully point out that in order for the reference to be considered anticipatory it must address every limitation found in the claim. As the Examiner astutely noted Maenpaa et al. teaches the administration of methoxsalen. Claims 21-23 require the use of a substance which selectively inhibits CYP2A6 and a substance which selectively inhibits CYP2B6. Maenpaa neither discloses or suggests the use of a substance which would selectively inhibit CYP2B6. Applicants respectfully request the rejection be withdrawn.

On pages 6 to 7 of the Office Action, the USPTO rejected claims 11, 12, 13, and 16 as anticipated by Garnitskij et al. (SU 1803032) based upon an oral translation of the reference. The USPTO contends that "Garnitskij et al. disclose a method for treating abstinence syndrome in tobacco dependence, the method comprising administering an effective amount of (0.2-0.5 ml) a 1% solution of pilocarpine HCL to the tongue of a human." (see, Office Action page 7). Applicants contend that the abstract is an insufficient reference. Applicants request the Examiner provide a full translation of the document from which the abstract is taken from if the Examiner wishes to use the reference. The Board recently held:

> [w]hen Applicants or their representatives cannot read the non-English

> language, however, they may not be able to form an adequate understanding of the reference to rebut the rejection on the merits or to amend the claims to avoid the reference. In such cases, Applicants should **insist that the examiner provide a translation** before a final rejection is entered, seeking supervisory intervention if necessary. (*Ex parte Bonfils*, 64 U.S.P.Q.2d 1456, 1461 (Bd. Pat. App & Interf. 2002)(Emphasis Added)(*See also infra*, *Ex parte Gavin*)(copies provided).

Additionally, the Board held:

> Generally an abstract does not provide enough information to permit an objective evaluation of the validity of what it describes. Thus, an abstract is even less reliable a basis to extrapolate the alleged teachings of the underlying document to different circumstances....**Citation of an abstract** without citation and reliance on the underlying scientific document itself is generally **inappropriate** where both the abstract and the underlying document are prior art. (*Ex parte Gavin*, 62 U.S.P.Q.2d 1680, 1684 (Bd. Pat. App & Interf. 2001)(Emphasis Added).

901.05(d)

Applicants request the Examiner utilize her discretion under MPEP 905.01(d) to obtain a written translation of the underlying document if the rejection is maintained. In the absence of a translation, Applicants respectfully request the rejection be withdrawn.

On page 7 of the Office Action, the USPTO rejected claims 7-9, 21-23 and 34-36 as being anticipated by Mays et al. To the extent applied against the claims as amended Mays et al. does not anticipate the current claim limitations. The Examiner states that Mays et al. "disclose a method of studying the effect of methoxsalen on caffeine metabolism by treating nonsmoking volunteers with psoriasis with an oral dose of 1.2 mg/kg methoxsalen." Applicants contend the reference does not suggest that such a pharmaceutical composition could regulate the metabolism of nicotine to cotinine as required by the claim. As clearly stated in the abstract and the top of page 622, second column, this study was performed on nonsmokers. This reference may in fact be viewed as teaching away from the claimed invention. Additionally, the treatment of psoriasis is not through chronic dosing, requires higher dosages of the methoxsalen, and acts through

photosensitivity.

Applicants contend that claim 21 is directed to a pharmaceutical composition comprising an effective amount of a composition to regulate the metabolism of nicotine to cotinine wherein the composition comprises at least two substances, at least one substance which selectively inhibits CYP2A6 and at least one substance which inhibits CYP2B6. Applicants respectfully point out that in order for the reference to be considered anticipatory it must address every limitation found in the claim. As the Examiner noted Mays et al. teaches the administration of methoxsalen. The claims 21-23 require the use of a substance which selectively inhibits CYP2A6 and a substance which selectively inhibits CYP2B6. Mays neither discloses or suggests the use of a substance which would selectively inhibit CYP2B6. Applicants respectfully request the rejection be withdrawn.

35 U.S.C. §103(a)

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

On pages 9 of the Office Action, the USPTO purports that claim 38 is obvious over Garnitskij et al. in view of Modi et al. The Examiner admits that Garniskij does not disclose adding an effective amount of a substance which 'inhibits' the metabolism of pilocarpine" and cites Modi et al. for the disclosure of antioxidants to pharmaceutical agents to prevent degradation of the agent. As Garnitskij is not a proper reference, and Modi et al. does not disclose the information purportedly found in Garnitsky, Applicants respectfully request the rejection be withdrawn.

CONCLUSION

Applicants assert that the above-referenced application is in condition for allowance. Reconsideration and allowance of all pending claims is respectfully requested. Should any

outstanding issues remain, the Examiner is invited to telephone the undersigned at 202-955-1500.

Respectfully submitted,

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Dated: Jan 9, 2003

Appendix A - Redline Version of the Claims

1. (Cancelled).

2. (Amended) The method ~~defined in~~ of claim 11 or 17, wherein CYP2A6 is selectively inhibited using one or more of the following (i) substances which inhibit CYP2A6 activity; or (ii) substances which inhibit transcription and/or translation of the gene encoding CYP2A6.

3. (Cancelled).

4. (Cancelled).

7. (Cancelled).

8. (Cancelled).

9. (Cancelled).

11. (Amended) A method for treating a condition requiring regulation of nicotine metabolism to cotinine in an individual comprising administering to ~~the subject~~said individual an effective amount of a substance which selectively inhibits CYP2A6.

12. (Amended) The method ~~defined in~~of claim 11, ~~wherein the substance is~~comprising at least one ~~compound~~ substance having a lactone structure with a carbonyl moiety.

13. ~~-~~(Amended)The method ~~defined in~~of claim 11, wherein ~~the substance is~~ at least one substance is ~~member selected from the group consisting of~~ coumarin, furanocoumarin, methoxsalen, imperatorin, psoralen, α-naphthoflavone, isopimpinellin, β-naphthoflavone, bergapten, sphondin, coumatetralyl (racumin), (+)-cis-3 ,5-dimethyl-2-(3-pyridyl)-thiazolidim-4-one, naringenin and related flavones, diethyldithiocarbamate, N-nitrosodialkylamine, nitropyrene, menadione, imidazole antimycotics, miconazole, clotrimazole, pilocarpine,

hexamethylphosphoramide, 4-methylnitrosamine-3-pyridyl-1 -butanol, aflatoxin B, analogs thereof and derivatives thereof.

16. (Amended) The method ~~defined in~~of any one of claims 11-15, wherein the condition is dependent or non-dependent tobacco use.

21. (Amended) A pharmaceutical composition ~~for use in treating a condition requiring regulation of nicotine metabolism to cotinine~~ comprising an amount effective ~~amount of a substance~~ to regulate the metabolism of nicotine to cotinine ~~which~~ wherein at least one substance selectively inhibits CYP2A6 and~~,~~ ~~an effective amount of an~~at least one substance inhibits~~or of~~ CYP2B6~~,~~ ~~and/or~~
~~a pharmaceutically acceptable carrier, diluent, or excipient~~.

22. (Amended) The composition ~~defined in~~of claim 21, ~~wherein the substance comprises~~comprising at least one substance having a lactone structure with a carbonyl moiety.

23. (Amended) The composition ~~defined in~~of claim 21, wherein ~~the substance comprises~~ at least one ~~member selected from the group consisting of~~substance is coumarin, furanocoumarin, methoxsalen, imperatorin, psoralen, α-naphthoflavone, isopimpinellin, β-naphthoflavone, bergapten, sphondin, coumatetralyl (racumin), (+)-cis-3 ,5-dimethyl-2-(3-pyridyl)-thiazolidim -4-one, naringenin and related flavones, diethyldithiocarbamate, N-nitrosodialkylamine, nitropyrene, menadione, imidazole antimycotics, miconazole, clotrimazole, pilocarpine, hexamethylphosphoramide, 4-methylnitrosamine-3-pyridyl-1-butanol, aflatoxin B, analogs thereof and derivatives thereof.

30. (Amended) The method ~~defined in any one~~ of claims ~~25-29~~, wherein the condition is dependent or non-dependent tobacco use.

34. (Cancelled).

35. (Cancelled).

36. (Cancelled).

38. (Amended) A method for treating a condition requiring regulation of nicotine metabolism to cotinine in an individual comprising administering to ~~the subject~~said individual: (a) an effective amount of a first substance which selectively inhibits CYP2A6; and (b) an effective amount of a second substance which is capable of ~~regulating inhibition~~ inhibiting the metabolism of the first substance.

39. (New) The method of claim 11, wherein the substance is methoxsalen or derivatives thereof.

40. (New) The method of claim 16, wherein the substance is methoxsalen or derivatives thereof.

41. (New) The method of claim 38, wherein at least one of said substances is methoxsalen or derivatives thereof.

42. (New) A method for reducing nicotine intake comprising administering to the subject in need of reduced nicotine intake a substance which selectively inhibits CYP2A6.

43. (New) The method of claim 42 comprising another substance capable of regulating inhibition of the first substance.

44. (New) The method of claim 42, wherein said substance delays metabolism of nicotine to cotinine.

Appendix C

Abstract

The invention relates to methods and compositions for regulating nicotine metabolism. Also provided are methods for screening and assessing substances for regulating nicotine metabolism. Methods are provided for assessing nicotine metabolism.

a13

Appendix B - Redline Version of the Specification

At page 10, line 22 extending to page 11, line 4:

Substances which inhibit transcription and/or translation of the gene encoding CYP2A6 include a nucleic acid sequence encoding the CYP2A6 gene (see Figure 2A, Genbank Accession No. HSU22027 (SEQ ID NO:1)) or parts thereof (e.g., the region which is about 20 nucleotides on either side of nucleotide 790 (ATG), and the splice sites 1237, 2115, 2499, 3207, 4257, 4873, 5577, and 6308), inverted relative to their normal orientation for transcription - i.e., antisense CYP2A6 nucleic acid molecules. Such antisense nucleic acid molecules may be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed with CYP2A6 mRNA or the CYP2A6 gene. The antisense sequences may be produced biologically using an expression vector introduced into cells in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense sequences are produced under the control of a high efficiency regulatory region, the activity of which may be determined by the cell type into which the vector is introduced.

At page 12, line 25 extending to page 13, line 2:

Substances which inhibit transcription and/or translation of the gene encoding CYP2B6 include a nucleic acid sequence encoding the CYP2B6 gene (see Figure 2B, GenBank Accession No. HSP452B6 for the mRNA sequence of CYP2B6 (SEQ ID NO:2), or parts thereof (e.g., the region which is on either side of nucleotide 9 (ATG), and the sites 111, 274, 424, 585, 762, 904, 1092, and 1234 nt), inverted relative to their normal orientation for transcription - i.e., antisense CYP2B6 nucleic acid molecules. Such antisense nucleic acid molecules may be produced and introduced into cells using conventional procedures as described herein.

At page 46, lines 12-18, please replace the Table with the following replacement Table:

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Sequence data for antisense oligodeoxynucleotides																								
NAME*	START*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	END	SEQ ID NO
ASO#15	-25	T	A	G	A	G	G	G	A	T	G	A	T	A	G	A	T	G	G	T	G	A	C	-4	3
ASO#13	171	C	T	T	C	A	T	G	A	G	G	G	A	G	T	T	G	T	A	C				189	4
ASO#25	190	G	G	C	C	A	T	A	G	C	G	C	T	C	A	C	T	G	A	T				208	5
ASO#23	333	C	C	A	T	A	G	C	C	T	T	T	G	A	A	G	A	C	C	C	A	G		353	6
MSO#23	333	C	C	C	C	A	G	C	C	T	T	T	G	A	A	G	A	C	A	T	A	G		353	7

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At page 47, lines 12-16:

Assay	Name	Sequence (5'-3')
CYP2A6*2 (v_1) and CYP2A6*3 (v_2)	F4	CCTCCCTTGCTGGCTGTGTCCCAAGCTTAGGC (SEQ ID NO: 8)
	R4	CGCCCCTTCCTTTCCGCCATCCTGCCCCCAG (SEQ ID NO: 9)
	E3F	GCGTGGTATTCAGCAACGGG (SEQ ID NO: 10)
	E3R	TCGTGGGTGTTTTCCTTC (SEQ ID NO: 11)

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FIG.2A CONT.

6721 ataatagcag ctcttatttc ctgagcacgt acccccgtgt caccttttgtt caaaaaccat
6781 tgcacgctca cctaatttgc cacaaaaccc ccttcgaagg ggcgttcatg cccattttac
6841 acgtgacaaa actgaggctt agaaagttgt ctctgatgtc tcacaaaaca taagtgccca
6901 gaaaatctgc gaacacagat ctgtgcccat agccttctag acagattctt aaaaagcacc
6961 tattcctcac gcaaaacagt ttagtataga atcacatggc ctgaacatcc ctgtccgggg
7021 gagttcccca gagacctggg gggtggttgc cctgccttca ctgcacacat gcccacactc
7081 tcacctactc aacatgctgt gactacccgg gtgtaatctg tgcttgctac cagataaggc
7141 cactgtagcc cattcagagt cagcccaggg acacaacgag acatgactgg acatacaggg
7201 tcagtccatt aacaa (SEQ ID NO:1)

FIG.2B CONT.

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  61 gaaaccttct gcagatggat agaagaggcc tactcaaatc ctttctgagg ttccgagaga
 121 aatatgggga cgtcttcacg gtacacctgg gacccaggcc cgtggtcatg ctgtgtggag
 181 tagaggccat acgggaggcc cttgtggaca aggctgaggc cttctctggc cggggaaaaa
 241 tcgccatggt cgacccattc ttccggggat atggtgtgat ctttgccaat ggaaaccgct
 301 ggaaggtgct tcggcgattc tctgtgacca ctatgaggga cttcgggatg ggaaagcgga
 361 gtgtggagga gcggattcag gaggaggctc agtgtctgat agaggagctt cggaaatcca
 421 agggggccct catggacccc accttcctct tccagtccat taccgccaac atcatctgct
 481 ccatcgtctt tggaaaacga ttccactacc aagatcaaga gttcctgaag atgctgaact
 541 tgttctacca gacttttca ctcatcagct ctgtattcgg ccagctgttt gagctcttct
 601 ctggcttctt gaaatacttt cctggggcac acaggcaagt ttacaaaaac ctgcaggaaa
 661 tcaatgctta cattggccac agtgtggaga agcaccgtga aaccctggac cccagcgccc
 721 ccaaggacct catcgacacc tacctgctcc acatggaaaa agagaaatcc aacgcacaca
 781 gtgaattcag ccaccagaac ctcaacctca acacgctctc gctcttcttt gctggcactg
 841 agaccaccag caccactctc cgctacggct tcctgctcat gctcaaataccctcatgttg
 901 cagagagagt ctacagggag attgaacagg tgattggccc acatcgccct ccagagcttc
 961 atgaccgagc caaaatgcca tacacagagg cagtcatcta tgagattcag agattttccg
1021 accttctccc catgggtgtg ccccacattg tcacccaaca caccagcttc cgagggtaca
1081 tcatccccaa ggacacagaa gtatttctca tcctgagcac tgctctccat gacccacact
1141 actttgaaaa accagacgcc ttcaatcctg accactttct ggatgccaat ggggcactga
1201 aaaagactga agcttttatc cccttctcct tagggaagcg gatttgtctt ggtgaaggca
1261 tcgcccgagc ggaattgttc ctcttcttca ccaccatcct ccagaacttc tccatggcca
1321 gccccgtggc cccagaagac atcgatctga caccccagga gtgtggtgtg ggcaaaatac
1381 ccccaacata ccagatccgc ttcctgcccc gctga (SEQ ID NO:2)
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